In the Abstract:

Attached hereto as page 30, pursuant to Rule 1.121(b)(1)(iii), is a marked-up version of the Abstract showing changes being made thereto. Attached hereto as page 31, pursuant to Rule 1.121(b)(1)(ii) is a clean version of the Abstract incorporating the changes being made thereto. Please replace the original Abstract with the new Abstract attached as page 31.

REMARKS

Claims 1-32 are pending herein. Claims 1-8 have been amended to correct matters of form. Attached hereto as pages 19-21, pursuant to Rule 1.121(c)(1)(ii), is a marked-up version of the amended claims.

New claims 9-32 are added hereby. Support for new claims 9-28 can be found on page 11, line 10-- page 12, line 10 of the specification. New claim 29 is supported by Fig. 17 of the present application. Support for new claims 30-32 can be found throughout the specification.

1. Claims 1-8 were rejected under §112, second paragraph, for the reasons stated in paragraphs 2a-n of the Office Action.

Claims 1-8 have been amended to more clearly recite the subject matter of the present invention. Before discussing paragraphs 2a-n of the Office Action, the preamble language recited in independent claims 1, 3 and 6 has been deleted from corresponding dependent claims 2, 4 and 7, respectively.

With respect to paragraph 2a, the term "based on" has been deleted from claims 1-8 and replaced with the term "containing."

With respect to paragraphs 2b and 2c, the preamble language in claims 1, 3, 5 and 6 has been changed from "a plurality of types of said capture solutions each of which specifically reacts with the specimen and each of which is used to obtain information on a structure of said specimen, wherein:" to --a plurality of types of said capture solutions each of which is adapted to specifically react with a specimen and provide information about a structure within the specimen, wherein:-- .

With respect to paragraphs 2d and 2e, the term "respectively" has been deleted from the language of claim 2, which now recites that the plurality of spots of capture solutions are formed from the same capture solution.

With respect to paragraphs 2f-2i, claim 3 has been amended to recite that the capture solution contains capture material and the concentration of the capture material in a plurality of spots of capture solutions varies from spot to spot. Claim 4, which depends from claim 3, has been amended to recite that the plurality of spots of capture solutions arranged on the base plate are formed from the same capture solution.

With respect to paragraph 2j, claim 5 has been amended to recite that each of the spots of capture solution has a plurality of types of capture material, and the spots are formed at a same spot formation position.

With respect to paragraph 2k, claim 6 has been amended to recite that each of the spots of capture solutions has a ratio between a major axis and a minor axis of not less than 0.9 and not more than 1.1.

With respect to paragraphs 2l and 2m, claim 7 has been amended to recite that the spots of capture solutions are arranged at least in a zig-zag configuration, and a ratio of an area on the base plate in which a spot is not arranged with respect to an inspection effective area on the base plate in which a spot is arranged is not more than 9%.

With respect to paragraph 2n, claim 8 is a product by process claim. This type of claim has long been held to be acceptable by the PTO. Moreover, applicants respectfully submit that claim 8 is not indefinite because it further limits claim 1 by reciting the specific process by which a spot of a capture solution is formed on a base plate.

For the reasons explained above with respect to original claim 8, Applicants respectfully submit that new product-by-process claims 9-28 also overcome any potential

§112, second paragraph rejection that might be asserted against those claims. New claims 9-14 correspond to original claim 8 and depend from claims 2-7, respectively. New claims 15-21 have also been added to depend from claims 2-7, respectively. Claims 15-21 recite that an ink-jet system is used to impact the spots onto the base plate after being discharged into the atmosphere, and wherein a force of the discharge is controlled electrically. Similarly, new claims 22-28 have been added to depend from claims 2-7, respectively. Claims 22-28 recite substantially the same limitations as new claims 15-21 with the addition that the number of times of discharge at each spot is electrically controlled.

In view of all of the foregoing, reconsideration and withdrawal of the §112, second paragraph rejection of claims 1-8 are respectfully requested.

2. Claims 1-5 and 8 were rejected under §102(e) over Felder et al. (U.S. Patent No. 6,232,066). This rejection is respectfully traversed.

The present invention is a DNA biochip array having increased detection sensitivity, which allows for the array to detect capture material (e.g., DNA, RNA or other biomolecules) in a target sample that is present in low concentrations. Detection sensitivity is increased by varying the spot sizes of capture solutions in the array (e.g., claim 1, discussed below) or varying the concentration of the capture material in each spot of capture solution (e.g., claim 3, discussed below). Accordingly, the presently claimed DNA biochip array makes it possible to offset inherent problems associated with the use of capture solutions, such as capture solutions having an inherently low ability to hybridize the capture material contained in certain genetic targets, for example.

The present invention is further advantageous in that it provides a greatly reduced arrangement area in which spots of capture solutions are formed on the base plate, which allows for the miniaturization of the DNA micro-array.

Independent claim 1 of the present invention recites, among other things, that a plurality of spots of capture solutions are formed on a base plate. The plurality of spots have different spot sizes. As explained above, independent claim 3 has been amended to recite that a plurality of spots of capture solutions are formed on a base plate in which the concentration of the capture material in the capture solution varies from spot to spot. Independent claim 5 has been amended to recite that each of the spots of capture solutions has a plurality of types of capture material, and the spots 80A and 80B are formed at a same spot formation position (see Figs. 16 and 17 of the present application).

With respect to claim 1, Felder et al. disclose a high throughput assay system in which mRNA targets are detected in 15 identical test regions, which are wells in a microtiter plate (column 3, lines 25-30). The PTO asserts that the assay system of Felder et al. uses a plurality of sample spots having different spot sizes. However, Applicants respectfully submit that Felder et al. disclose that oligonucleotide anchors are provided that can be attached to particles, beads or the like that can be formed to be different in size or shape from one another (column 8, lines 52-56). As such, Felder et al. merely disclose that a bead or particle size is varied, but wherein each bead has a ***fixed*** amount of capture solution disposed thereon. Consequently, Applicants can find no disclosure or suggestion of forming a plurality of sample spots on Felder's beads "which have different spot sizes" (i.e., varying the volumes of each sample spot), as recited in independent claim 1.

With respect to claim 3, Felder et al. disclose that oligonucleotide anchors can be arranged in a bar code pattern (column 8, line 16-28). In this respect, Felder et al. teach a pattern recognition technique for defining the positioning of separate oligonucleotide anchors (column 8, lines 24-28). Applicants respectfully submit that even though each bar code area comprises a different pattern, there is no disclosure in Felder et al. of varying the

concentration of the capture material from bar code line to bar code line. Applicants respectfully submit that the §102 rejection of claim 3 over Felder et al. is erroneous because claim 3 recites that the concentration of the capture material in the capture solution varies from spot to spot. This feature is simply not disclosed in Felder et al.

With respect to independent claim 5, Felder et al. disclose that separate wells include at least 8 different oligonucleotide anchors each having linker molecules which include a first portion specific for the oligonucleotide anchor and a second portion specific for a target in a sample solution (column 2, lines 49-62). Even though Felder et al. disclose the use of oligonucleotide anchors attached to the surface of each well, Applicants could find no disclosure in Felder et al. of a plurality of oligonucleotide anchors being formed at a same spot formation position. Rather, Felder's oligonucleotide anchors are attached at ***different*** spot formation positions within each sample well. For example, Fig. 1 of Felder et al. clearly shows that each test region contains six different oligonucleotide anchors, which are illustrated by numbers 1-6 (column 3, lines 30-32). Therefore, Applicants respectfully submit that Felder et. al. do not disclose or suggest forming sample spots "at a same spot formation position," as recited in claim 5.

In view of all of the foregoing, reconsideration and withdrawal of the rejection of claims 1-5 and 8 under §102(e) over Felder et al. are respectfully requested.

3. Claims 3-6 were rejected under §102(e) over Hyldig-Nielsen et al. (U.S. Patent No. 6,280,946). This rejection is respectfully traversed.

Hyldig-Nielsen et al. disclose a chemiluminescent *in situ* hybridization procedure performed on a nylon membrane. The sample is filtered onto the membrane to isolate and separate individual microorganisms. A dilution row containing different concentrations of rRNA from each of the cultured bacteria is blotted onto the nylon membrane. The nylon

membrane is then air dried, UV-cross linked and stored in a plastic bag until used. Upon use of the nylon membrane to detect bacterial contamination in a target sample, a series of hybridization steps are carried out to allow PNA (peptide nucleic acid) probes to hybridize with complimentary genetic components on the bacteria affixed to the nylon membrane. Excess PNA probes are then removed by washing, and the hybridized probes are visualized by a chemiluminescent reaction followed by film exposure. In this manner, each colony of bacteria can be observed.

With respect to claim 3, the PNA probes disclosed in Hyldig-Nielsen et al. are not formed on a base plate. Rather, the PNA probes are suspended in liquid and applied to a nylon membrane containing the target sample (i.e., microorganism rRNA) sought to be hybridized. Moreover, Hyldig-Nielsen et al. teach varying the concentration of the target sample to obtain the desired hybridization with the complimentary PNA probe, and do not disclose differing the concentration of the capture material in the capture solution from spot to spot, as recited in claim 3.

With respect to claim 5, as explained above, there is no disclosure in Hyldig-Nielsen et al. that the PNA probes (i.e., capture solutions) are arranged on a base plate. Secondly, Applicants can find no disclosure in Hyldig-Nielsen et. al. that either of the target rRNA (bacteria/eucarya) or the PNA probes are "formed at a same spot formation position," as shown in Figs. 16 and 17, and recited in claim 5.

In addition, Applicants respectfully submit that there is no disclosure in Hyldig-Nielsen of the features recited in new claim 29, which depends from claim 5. With reference to Fig. 17 of the present application, a first layer spot 80A comprises a ridged peripheral portion 120 and a second layer spot 80B is deposited on the first layer spot inside the ridged

peripheral portion. No such structure is disclosed in Hyldig-Nielsen. Accordingly, at least new claim 29 should be indicated as allowable.

With respect to claim 6, the arguments asserted above against Hyldig-Nielsen et al. apply equally as well here. In addition, independent claim 6 recites that each of the spots of capture solutions has a ratio between a major axis and a minor axis of not less than 0.9 and not more than 1.1. The above numerical limitation recited in claim 6 defines the degree of roundness of the capture solution spots. Applicants respectfully submit that Hyldig-Nielsen et al. are completely silent regarding the claimed ratio. Moreover, the PTO has provided no evidence that the RNA of the microorganisms spotted onto the nylon membrane, which is permeable, disclosed in Hyldig-Nielsen et. al. would necessarily disclose the claim numerical limitation recited in claim 6.

New dependent claims 30-32 depend from claims 3, 5 and 6, respectively, and have been added to further distinguish the present application over Hyldig-Nielsen et al. For example, each of new claims 30-32 recite that the base plate is non-permeable with respect to the capture solution. Applicants respectfully submit that Hyldig-Nielsen et al. disclose a membrane (i.e., nylon) that is permeable with respect to the capture solution. Accordingly, at least claims 30-32 should be indicated as allowable.

In view of all of the foregoing, reconsideration and withdrawal of the §102 rejection of claims 3-6 over Hyldig-Nielsen et al. and allowance of new claims 29-32 are respectfully requested.

4. Claims 5 and 6 were rejected under §102(b) over Brown et al. (U.S. Patent No. 5,807,522). This rejection is respectfully traversed.

Brown et al. disclose a method of forming a micro array of analyte-specific assay regions on a solid support. A dispenser is positioned above the solid support and a dispenser tip is moved rapidly toward and away from the substrate surface, making momentary contact

with the surface, in effect, tapping the tip of the dispenser against the support surface. The tapping movement of the tip against the surface acts to break the liquid meniscus in the tip channel, bringing the liquid in the tip into contact with the support surface (see Figs. 2A-2C).

With respect to claim 5, similar to the disclosure in Felder et al., Brown et al. disclose that each distinct bipolymer is disposed at a separate, defined position in the array (column 4, lines 15-24). Therefore, Applicants respectfully submit that the different analyte-specific reagents disclosed in Brown et al. are not formed "at a same spot formation position," as recited in claim 5.

With respect to claim 6, as explained above, Brown et al. employ a method of spot formation wherein the tip of the dispenser physically contacts a base plate (Figs. 2A-2C). As such, spot formation is easily affected by the dispenser, and the shape of the spot is highly result dependent. Accordingly, Applicants respectfully submit that the spots of reagent solution disclosed in Brown et al. do not explicitly or necessarily disclose spots having a ratio between a major axis and a minor axis of not less than 0.9 and not more than 1.1, as recited in claim 6.

In view of all of the foregoing, reconsideration and withdrawal of the §102 rejection of claims 5 and 6 over Brown et al. are respectfully requested.

5. Claim 7 was rejected under §103(a) over Brown et al. in view of Fisher (U.S. Patent No. 6,232,072). Applicants respectfully submit that the arguments submitted above distinguish claim 6 from Brown et al. Since Fisher does not overcome the deficiencies of Brown et al., and since claim 7 depends directly from claim 6, claim 7 is also believed to be allowable over the applied art.

For all of the foregoing reasons, Applicants respectfully submit that all pending claims herein are in condition for allowance. Accordingly, the Examiner is requested to issue a Notice of Allowance for this application in due course.

If the Examiner believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, the Examiner is herein requested to call Applicants' attorney at the phone number noted below.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

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Date

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1. (Amended) A biochip comprising a large number of spots ~~based on~~containing capture solutions arranged on a base plate, obtained by supplying, onto said base plate, a plurality of types of said capture solutions each of which is adapted to specifically reacts with a specimen and ~~each of which is used to obtain~~provide information ~~on~~about a structure ~~of said~~within the specimen, wherein:

a plurality of said spots, which have different spot sizes, are formed on said base plate.

2. (Amended) A biochip according to claim 1, ~~comprising a large number of spots based on capture solutions arranged on a base plate, obtained by supplying, onto said base plate, a plurality of types of said capture solutions each of which specifically reacts with a specimen and each of which is used to obtain information on a structure of said specimen,~~ wherein:

~~a~~said plurality of ~~said~~ spots~~, which have different spot sizes on said base plate respectively,~~ are formed ~~for captures of an identical type~~from the same capture solution.

3. (Amended) A biochip comprising a large number of spots ~~based on~~of capture solutions containing a capture material therein arranged on a base plate, obtained by supplying, onto said base plate, a plurality of types of said capture solutions each of which is adapted to specifically reacts with a specimen ~~and each of which is used to obtain~~and provide information ~~on~~about a structure ~~of said~~within the specimen, wherein:

a plurality of said spots are formed~~,~~ in which ~~an amount of a capture per unit area immobilized in each of said spots differs~~the concentration of the capture material

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Amended Claims

in the capture solution varies from spot to spot.

4. (Amended) A biochip according to claim 3, ~~comprising a large number of spots based on capture solutions arranged on a base plate, obtained by supplying, onto said base plate, a plurality of types of said capture solutions each of which specifically reacts with a specimen and each of which is used to obtain information on a structure of said specimen,~~ wherein~~:~~

a said plurality of ~~said~~ spots~~, which have different amounts of said capture per unit area immobilized on said base plate respectively,~~ are formed ~~for captures of an identical type~~ from the same capture solution.

5. (Amended) A biochip comprising a large number of spots ~~based on~~ containing capture solutions arranged on a base plate, obtained by supplying, onto said base plate, a plurality of types of said capture solutions each of which is adapted to specifically reacts with a specimen and ~~each of which is used to obtain~~ provide information ~~on~~ about a structure ~~of said~~ within the specimen, wherein:

each of said spots~~, which are composed of different~~ has a plurality of types of ~~said captures, are~~ capture material, and said spots are formed at ~~an identical~~ a same spot formation position.

6. (Amended) A biochip comprising a large number of spots ~~based on~~ containing capture solutions arranged on a base plate, obtained by supplying, onto said base plate, a plurality of types of said capture solutions each of which is adapted to specifically reacts with a specimen and ~~each of which is used to obtain~~ provide information ~~on~~ about a structure ~~of said~~ within the specimen, wherein:

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Amended Claims

each of said spots has ~~a shape of a substantially circular configuration, and~~ a ratio between a major axis and a minor axis of ~~said substantially circular configuration is~~ not less than 0.9 and not more than 1.1.

7. (Amended) A biochip according to claim 6, ~~comprising a large number of spots based on capture solutions arranged on a base plate, obtained by supplying, onto said base plate, a plurality of types of said capture solutions each of which specifically reacts with a specimen and each of which is used to obtain information on a structure of said specimen,~~ wherein:

said spots are arranged at least in a zigzag configuration, and a ratio of an area on said base plate in which said spots ~~is~~are not arranged~~deposited~~ with respect to an inspection effective area on said base plate in which said spots are arranged is not more than 9 %.

8. (Amended) A biochip according to ~~claim any one of~~ claims 1~~, to 7~~, wherein said spots ~~based on~~of said sample solution are formed by means of an ink-jet system.

VERSION WITH MARKINGS TO SHOW CHANGES MADE
Amended Claims

Paragraph beginning at line 4 of page 1 has been amended as follows:

~~TECHNICAL FIELD~~FIELD OF THE INVENTION

The present invention relates to a DNA microarray (DNA chip) which specifically reacts with a biochemical specimen and which is used for inspection equipment represented, for example, by a biochip to be used in order to obtain information on a structure of the specimen, especially in which several thousands to not less than ten thousands kinds of different types of DNA fragments are aligned and fixed at a high density as spots on a base plate such as a microscopic glass slide ~~glass~~.

Paragraph beginning at line 15 of page 1 has been amended as follows:

~~BACKGROUND ART~~BACKGROUND OF THE INVENTION

The method of analyzing the genetic structure has been remarkably progressed in recent years. A large number of genetic structures represented by those of human genes have been clarified. The analysis of the genetic structure uses a DNA microarray (DNA chip) in which several thousands to not less than ten thousands kinds of different types of DNA fragments are aligned and fixed as spots on a base plate such as a microscopic glass slide ~~glass~~.

Paragraph beginning at line 24 of page 1 has been amended as follows:

In recent years, there is a demand for enhancing the reproducibility, the quantitative performance in the information obtained from the DNA microarray and obtaining much more information from the DNA microarray. The information obtained from respective spots needs to be correct, uniform, and complex.

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Specification Paragraphs

Paragraph beginning at line 17 of page 2 has been amended as follows:

The conventional method of forming the spot is based on the supply (stamping) of the sample solution onto the base plate by using the pin. Therefore, the shape of the spot is diversified, for example, due to the shape of the forward end of the pin and/or the residue of the sample solution remaining at the forward end of the pin after the supply. As shown in FIG. 18, spots 200, each of which has ~~a lot of~~many irregularities at the outer circumferential portion, are formed on a base plate 202.

Paragraph beginning at line 9 of page 3 has been amended as follows:

The present invention has been made taking the foregoing problems into consideration, an object of which is to provide a DNA microarray which makes it possible to improve the inspection accuracy for ~~the~~ genetic ~~analysis~~analyses and which makes it possible to increase the amount of information to be obtained.

Paragraph beginning at line 15 of page 3 has been amended as follows:

Another object of the present invention is to provide a DNA microarray which makes it possible to achieve a high degree of concentration of spots and which makes it possible to perform detailed genetic ~~analysis~~analyses.

Paragraph beginning at line 7 of page 4 has been amended as follows:

~~DISCLOSURE~~SUMMARY OF THE INVENTION

The present invention lies in a biochip comprising a large number of spots based on capture solutions arranged on a base plate, obtained by supplying, onto the base plate, a plurality of types of the capture solutions each of which specifically reacts with a specimen and each of which is used to obtain information on a structure

of the specimen; wherein a plurality of the spots, which have different spot sizes, are formed on the base plate.

Paragraph beginning at line 24 of page 11 has been amended as follows:

Especially, the amount of the capture per unit volume is preferably varied by discharging and supplying the capture solution a plurality of times to one spot on the base plate in accordance with the ink-jet system. That is, the capture solution is discharged and supplied a plurality of times in a divided manner without discharging and supplying a large amount of the capture solution at once. Further, the discharge interval is adjusted so that ~~the~~a previously formed spot ~~formed by one time of discharge~~ is not widened in spot diameter due to superimposition of the capture solution subsequently discharged ~~next time~~. Accordingly, the amount of the capture supplied to the spot can be increased or decreased without changing the size of the spot. Thus, it is possible to vary the capture density per unit area.

Paragraph beginning at line 11 of page 14 has been amended as follows:

~~BEST MODE FOR CARRYING OUT THE INVENTION~~DETAILED DESCRIPTION OF THE DRAWINGS

Embodiments of the DNA microarray ~~included in embodiments of the biochip~~ according to the present invention will be explained below with reference to FIGS. 1 to ~~2~~218.

Paragraph beginning at line 12 of page 16 has been amended as follows:

The precipitated DNA fragments are rinsed with ethanol, followed by centrifugation. After that, the DNA fragments are dried to produce the DNA powder

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Specification Paragraphs

(purification step S12). A certain amount of x1 TE buffer is added to the obtained DNA powder, followed by being left to stand for several hours to completely dissolve the DNA powder (mixing step S13). Thus, the sample solution is prepared. The concentration of the sample solution at this stage is 0.1 to 10 μg/~~μ liter~~ml.

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Specification Paragraphs

When ~~the~~ genetic ~~analysis is~~analyses are performed ~~by~~ using ~~a~~the DNA microarray of the present invention, the inspection accuracy is improved. A sample solution is supplied onto a base plate 10 to prepare the DNA microarray 20 ~~comprising~~which includes a large number of spots 80 ~~based on the sample~~containing capture solutions arranged on the base plate 10. The capture solutions are adapted to specifically react with a specimen and provide information about a structure within the specimen. In the microarray 20, the planar configuration of the spots 80 ~~is~~are substantially circular, and a plurality of spots having different spot sizes are formed on the base plate.

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Abstract